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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,295	10/15/2001	Avi Ashkenazi	GNE.2630P1C11	6495

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,295	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 May 2005 has been entered.

It is noted that the previous Advisory Action (mailed 15 October 2004) failed to indicate whether the after final amendment received 28 July 2004 was entered or not. Applicant is advised that the after final amendment was entered.

Claims 1-57 and 63 are canceled. Claims 58-62 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 58-62 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Claims 58-62 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejection is set forth in the previous Office Actions. See, for example, the non-final rejection mailed 04 February 2004.

Applicant's arguments (pp. 5-17 of the preliminary amendment received 20 May 2005) have been fully considered but are not fond to be persuasive for the following reasons. The Goddard declaration under 37 CFR 1.132 filed 20 May 2005 is insufficient to overcome the rejection of claims 58-62 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons.

Applicant reviews the legal standard for patentable utility, with which the examiner takes no issue.

Applicant argues that the gene amplification assay is well-described in Example 143 (it is assumed that applicant intended assay 114, Table 9), showing that nucleic acids encoding PRO351 were increased more than 2 fold I lung tumors LT9, LT10, LT11, LT13, LT15, LT16, LT17, LT18, LT19, and LT21. Applicant argues that the PRO351 nucleic acid was amplified in a significant number of lung tumors and showed a significant increase in DNA copy number in these tumors. This has been fully considered but is not found to be persuasive. While the data in Table 9 may provide a basis for utility and enablement of PRO351 nucleic acid, it does not provide a basis for utility or enablement of the claimed antibodies, whose utility depends upon whether or not the polypeptides they bind have utility. The art supports this position by establishing that there is no strong correlation between gene amplification and increased mRNA or

protein levels. See Haynes et al., Pennica et al., Konopka et al. of record. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay does not provide a comparison between the lung tumor samples and normal lung epithelium, and thus it is not clear that PRO351 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO351 is a diagnostic probe for lung cancer unless it is clear that PRO351 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Also, while it might be argued in hindsight that PRO351 would still be a marker at least for precancerous, or damaged, lung epithelium, such is not suggested by the specification as originally filed and is not well-established in the *prior* art.

Applicant points to the Goddard declaration as stating that an at least 2 fold increase in gene copy number in a tumor tissue sample relative to a normal sample is significant, and that the gene can be used as a diagnostic marker. This has been fully considered but is not found to be persuasive, since the claims are directed to antibodies, not genes. A change in gene copy number does not reliably correlate with a change in polypeptide expression levels (which can be detected by the claimed antibodies), as evidenced by the references cited herein. Furthermore, Table 9 reports a comparison of lung tumor tissue samples with a pooled sample of DNA from normal

cells, but not matched tissue samples (i.e., normal lung epithelium tissue). The Goddard declaration states that a 2 fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant. However, it is not clear if Dr. Goddard intended the phrase "normal samples" to include unrelated tissue samples such as those used in the specification. The art uses matched tissue samples as a rule when evaluating whether or not a protein (or its antibodies) can be used as a diagnostic for cancer, indicating that the art does not consider pooled, unrelated DNA samples to be an appropriate control. See Hu et al. (2003, Journal of Proteome Research 2:405-412) and Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313).

Applicant criticizes Pennica et al. and Konopka et al. as being limited to only one gene. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. constitute evidence that one skilled in the art cannot assume that any one gene's amplification results in protein over-expression. The issue at hand also concerns only one gene, the protein it encodes, and antibodies that bind the protein.

Applicant criticizes Haynes et al., stating that there is no legal requirement to establish a necessary or strong correlation between an increase in copy number of mRNA and protein expression levels. Applicant argues that the issue is whether or not it is more likely than not that a person of ordinary skill in the pertinent art would recognize a positive correlation between mRNA expression levels and protein expression levels. Applicant argues that there is a positive correlation between most of the 80 proteins studied by Haynes et al. Applicant argues that Haynes et al. is not relevant because it is limited to yeast genes, not human genes. Applicant argues that

Haynes et al. failed to compare mRNA expression levels and protein expression levels in the same yeast cells. Applicant concludes that the reliance on Haynes et al. is misplaced, since it shows a general trend between mRNA and protein levels, and that an improper, heightened legal standard has been applied. This has been fully considered but is not found to be persuasive. Haynes et al. clearly conclude that, "even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, section 2.1). Regarding the relevance of yeast genes, Applicant is directed to Lian et al. (2001, Blood 98:513-524) who show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). The evidence as a whole clearly indicates that one skilled in the art would not assume that an increase in gene copy number would correspond with an increase in mRNA levels or protein levels without doing the empirical experimentation necessary to measure mRNA and protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed antibodies is not substantial; it is not in currently available form.

Applicant discusses the Orntoft, Hyman and Pollack references. Orntoft et al. (Molecular and Cellular Proteomics1:37-45, 2002) *could only compare the levels of about 40 well-resolved and focused abundant proteins."* (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of low levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO351 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification.

Applicant refers again to the Polakis declaration, and argues that the examiner's criticism of the declaration for failing to provide data is improper. However, given the evidence in the art that increased DNA amplification does not necessarily correlate with increased mRNA levels, and that increased mRNA levels do not necessarily correlate with increased protein levels, the examiner maintains that one skilled in the art would

view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO351 are specifically amplified in tumors. Further research would have to be done in order to determine if PRO351 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to indicate PRO351 protein as a cancer marker.

Applicant argues that the examiner must accept an opinion from a qualified expert. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the nature of the fact is whether or not there is a correlation between mRNA levels and protein levels. There is strong opposing evidence that there is no strong correlation between the two. The expert has a strong interest in the outcome of the case, as Dr. Polakis is employed by the assignee. Finally, while Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicant criticizes the examiner's reliance on Hu et al. Applicant argues that Hu et al. is not relevant, as it does not discuss gene amplification. Applicant criticizes Hu et al. as being base don a statistical analysis of information published in the literature. This ahs been fully considered but is not found to be persuasive. The asserted utility for the claimed antibodies is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins (and their antibodies) as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO351 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO351 protein, or its antibodies, can be used as a cancer diagnostic. Furthermore, Applicant's attention is directed to Hanna et al. (of record, Pathology Associates Medical Laboratories, 1999), who show that gene

amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, the asserted utility is not substantial.

Applicant criticizes Hu et al. as using faulty statistical analysis. This has been fully considered but is not found to be persuasive. Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc.

It is important to note that the specification does not actually assert that the claimed antibodies can be used as cancer diagnostics in Example 114. Rather, it is asserted that the antibodies can be used to develop cancer therapeutics. However, this asserted utility is not substantial, since the specification does not provide a clear nexus between PRO351 and cancer occurrence or progression, for reasons noted above.

Thus, the preponderance of the art supports the *prima facie* finding that a minor amplification of DNA would not form the basis for a substantial assertion of an association between PRO351 protein and cancer.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (571) 272-0829. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER